Recent Advances in the Management of Adenocarcinoma of the Small Intestine

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ABSTRACT

Adenocarcinoma of the small intestine is a rare malignancy with limited data available to guide therapeutic decisions. Delays in diagnosis are frequent and the majority of patients will present with advanced-stage disease and either lymph node involvement or distant metastatic disease. Furthermore, the role of adjuvant therapy in patients who undergo curative resection is unclear. Recent retrospective and prospective studies have helped to clarify the optimal chemotherapy approach for advanced small bowel adenocarcinoma. The combination of capecitabine and oxaliplatin is highly active, with a median overall survival of 15 months in patients with metastatic disease. Further clinical studies in this rare tumor type are needed. This article reviews the clinical features and evaluation of patients with small bowel adenocarcinoma and focuses on recent advances in management.

Gastrointest Cancer Res 3:90–96.

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Submitted: February 3, 2009
Accepted: April 20, 2009

It is estimated that a total of 6,110 new cases of small bowel cancer will have been diagnosed in the United States in 2008.[1] Historically, adenocarcinomas have been the most common histologic subtype, representing 30%–50% of malignant small bowel tumors. However, because of a steady rise in the incidence of carcinoid tumors over the past few decades, carcinoid tumors are now the most common cancer of the small bowel. According to the National Cancer Data Base from 2005, the distribution of histologic subtypes of small bowel cancer were as follows: carcinoid in 44%, adenocarcinoma in 33%, lymphoma in 15%, and gastrointestinal stromal tumor (GIST) in 7%.[2]

In contrast to adenocarcinoma of the large intestine, the incidence of adenocarcinoma of the small intestine is approximately forty- to fiftyfold less common.[1] This difference occurs despite the small intestine representing approximately 70%–80% of the length and 90% of the surface area of the alimentary tract.[3] The rarity of the disease has severely limited both clinical and molecular understanding of this cancer.

ETIOLOGY

Little information is available regarding the molecular etiology of small bowel adenocarcinoma, though similarities among both genetic and environmental factors between large and small intestinal cancer have suggested a similar process of carcinogenesis at both sites. According to an analysis of the Surveillance, Epidemiology and End Results (SEER) database, patients who develop either a small or large intestine adenocarcinoma are at increased risk for a second cancer at either intestinal site.[4] In addition, the inherited genetic cancer syndromes of hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) result in an increased risk for both large and small intestine adenocarcinoma. As seen with colorectal cancer, diets high in red meat are associated with an increased risk of small bowel adenocarcinoma, whereas diets high in vegetables or dietary fiber have a protective effect.[5–7]

Adenocarcinomas of the small intestine appear to undergo a similar phenotypic adenoma-carcinoma transformation, as seen in colorectal cancer.[8,9] However, in contrast to the large intestine, adenomas of the small intestine are rare.[10] Molecular analysis of small bowel adenocarcinomas has demonstrated the presence of high or low microsatellite instability (MSI) in approximately 20% of cases.[11] Methylation of hMLH1 and either germline or sporadic loss of mismatch repair proteins have all been reported in cases with MSI.[11–13] Therefore, as seen in colorectal cancer, a subset of small intestine adenocarcinomas appear to be driven by defects in DNA mismatch repair. Abnormalities in p53 and KRAS are common, with p53 overexpression in 40%–52% of cases and KRAS mutations in 40%–53% of cases.[12,14,15]

One of the most marked differences, in comparison to colorectal cancer, is the infrequent rate of mutations in the adenomatous polyposis coli (APC) gene. Chromosomal loss of 5q has been reported in 10%–18% of cases, and mutations in APC have been reported in 3 of 57 cases.[14,16,17] Mutations in beta-catenin, another member of the Wnt signaling pathway, occur in 5% of patients.[16]

A number of theories have been proposed to explain the small intestine's relative protection from the development of carcinoma, but none have been definitively proven. Proposed protective factors have generally centered around two concepts. First, the rapid turnover time of small intestinal cells results in epithelial cell shedding prior to the accumulation of genetic

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Table 1. TNM staging for adenocarcinoma of the small intestine

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor invades lamina propria or submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor invades through muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) with extension 2 cm or less*		
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery, or retroperitoneum more than 2 cm, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas)		
Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
	T4	N0	M0
Stage III	Any T	N1	M1
Stage IV	Any T	Any N	M1

Adapted from AJCC Cancer Staging Manual, Sixth Edition
*The peritonealized perimuscular tissue is for the jejunum and ileum, part of the mesentery; and for duodenum in areas where serosa is lacking, part of the retroperitoneum

damage. Second, exposure to the carcinogenic components of our diet are limited due to a rapid small bowel transit time, lack of bacterial degradation activity, and the relatively dilute alkaline environment of the small bowel. Recent molecular data regarding the low rate of APC mutations support the hypothesis that the dramatic difference in cancer rate between the small and large intestine may relate to an inherent resistance of small intestinal enterocytes to the development of APC mutations and subsequent adenoma formation.[18]

Further investigation into the molecular abnormalities and carcinogenesis of small intestinal adenocarcinoma is needed, as such knowledge would likely provide insights into the understanding of the much more common adenocarcinoma of the colon.

EPIDEMIOLOGY

According to a review of 25,053 patients from the National Cancer Data Base, the sites of small bowel involvement are as follows: 56% duodenum, 16% jejunum, 13% ileum, and 15% not identified.[2] The incidence of small bowel adenocarcinoma peaks in the seventh and eighth decades of life, with a mean age of 65 years. Earlier presentations are seen in those patients with predisposing conditions such as HNPCC, FAP, inflammatory bowel disease (IBD), or celiac disease.

CLINICAL PRESENTATION

Symptoms of small bowel adenocarcinoma are nonspecific and frequently do not occur until advanced disease is present. A number of retrospective studies have noted delays in diagnosis ranging from 4 to 7 months.[19,20] The most commonly reported symptoms are abdominal pain, nausea/vomiting, weight loss, and gastrointestinal bleeding. Staging for small bowel adenocarcinoma is according to the American Joint Committee on Cancer (AJCC) guidelines, which is based on the TNM staging system (Table 1).[21] The presenting stage distribution according to the National Cancer Data Base was stage I in 12%, stage II in 30%, stage III in 26%, and stage IV in 32%.[2]

DIAGNOSIS

Until recently, evaluation of the entire small intestine was a challenge. A barium small bowel follow-through has been the radiographic gold standard for small bowel evaluation. Limited retrospective data in patients with advanced-stage disease have demonstrated an approximate sensitivity of 60% for the diagnosis of small bowel tumors.[22,23] Cross-sectional imaging with either computed tomography (CT) or magnetic resonance imaging (MRI) provides useful information regarding local-regional nodal involvement or distant metastatic disease but has limited ability to identify primary lesions, with sensitivities in the literature ranging from 47%–80%.[24,25] The addition of enteroclysis, which involves the infusion of contrast material directly into the small intestine via a nasogastric tube, or the use of novel high-volume neutral oral contrast agents, can result in improved sensitivity for the detection of small bowel lesions, but it is not widely available.[26]

Endoscopic evaluation of the small bowel has been limited by the length of the small intestine, which can measure up to five meters. Push enteroscopy, which involves the examination of the small bowel with a long enteroscope, is generally only able to visualize the proximal 150–200 cm of small bowel. Double-balloon enteroscopy is able to visualize the entire small bowel, though it is time consuming and only available at specialized centers. A number of small studies using double-balloon enteroscopy have reported the identification of small bowel pathology, including small bowel adenocarcinoma, following extensive workups that have included the use of wireless capsule endoscopy.[27,28]

The incorporation of wireless capsule endoscopy, first approved in the United States in 2001, has allowed a much simpler and improved method for evaluating the lumen of the small intestine. This

Table 2. Poor prognostic factors from multivariate analyses

Study	Time period	No. pts	Multivariate factors
Small intestine			
Bilimoria[2]	1985–2005	25,053	Age >55 years Male Black ethnicity Duodenal or ileal location T4 tumor stage Lymph node involvement Metastatic disease Poor differentiation Positive margins
Howe[34]	1985–1995	4,995	Regional or distant disease Age >75 years Duodenal location Poor differentiation
Dabaja[36]	1978–1998	217	Lymph node ratio >75% Curative resection
Wu[53]	1983–2003	80	TNM stage III/IV Curative resection Lymph node involvement
Agrawal[37]	1971–2005	64	T4 tumor stage Non-curative resection Metastatic disease
Duodenum			
Rose[54]	1983–1994	79	Metastatic disease Non-curative resection
Bakaeen[55]	1976–1996	68	TNM stage III/IV Positive margins Weight loss Lymph node involvement

technique has been primarily applied to the evaluation of obscure gastrointestinal bleeding, where it has shown superiority over other imaging and endoscopic techniques.[29]

In a large retrospective review of 562 patients who underwent capsule endoscopy for various reasons at Mount Sinai Hospital from 2001 to 2003, small bowel tumors were found in 8.9% of cases.[30] In patients younger than 50 years old who underwent capsule endoscopy for evaluation of obscure gastrointestinal bleeding, the rate of diagnosing small bowel tumors rose to 13%.

In a study evaluating capsule endoscopy in 60 patients with suspected small bowel pathology, but without gastrointestinal bleeding, the overall diagnostic yield of capsule endoscopy was 62%.[31] In this study, all patients had undergone upper and lower gastrointestinal endoscopy, and many had undergone enteroclysis, small bowel follow-through, push enteroscopy, and abdominal CT.

In a meta-analysis evaluating 32 studies in which capsule endoscopy was prospectively evaluated against a comparator technique (push enteroscopy, small bowel series, or colonoscopy with ileoscopy), a total of 106 neoplasms were identified.[29] Capsule endoscopy identified 81% of these lesions while the comparator technique identified only 37%.

For tumors of the duodenum, endoscopic ultrasound (EUS) can be useful in assessing both the depth of invasion and nodal status. Although not directly studied for duodenal adenocarcinoma, the use of EUS has demonstrated improvements in staging accuracy when applied to the evaluation of ampullary and pancreatic cancers.[32,33]

PROGNOSIS AND PATTERNS OF FAILURE

In a review from the National Cancer Data Base, from 1985 to 1995 5-year disease-specific survival by stage was 65% for stage I, 48% for stage II, 35% for stage III, and 4% for stage IV.[34] The various factors that have been associated with poor prognosis in multivariate analyses from the literature are reported in Table 2. Advanced disease stage, poor histologic differentiation, elderly age, duodenal primary, and positive margins are associated with a worse prognosis. Whether the poor outcome for duodenal adenocarcinomas relates to the complex retroperitoneal anatomy of the duodenum or to an intrinsic difference in tumor biology from jejunal and ileal tumors is not known. Other

Table 3. Patterns of recurrence following definitive surgical resection

Study	Time period	No. resected	No. relapsed		Pattern of relapse			
			Total	(%)	Local	(%)	Distant	(%)
Small intestine								
Agarwal[37]	1971–2005	30	21	(70)	6	(29)	20	(95)
Wu[53]	1983–2003	43	19	(44)	0	(0)	19	(100)
Dabaja[36]	1978–1998	146	56	(38)	10	(7)	48	(33)
Bauer[56]	1971–1991	38	32	(84)	6	(19)	26	(81)
Duodenum								
Kelsey[57]	1975–2005	31	NR		12		13	
Swartz[58]	1994–2003	14	7	(50)	1	(14)	7	(100)
Bakaeen[55]	1976–1996	68	25	(37)	14	(56)	21	(84)
Barnes[59]	1967–1991	36	18	(50)	6	(33)	12	(66)

Abbreviations: No. = number; NR = not reported

Table 4. Studies of adjuvant therapy for small bowel adenocarcinoma

Author	Time period	Institution/ organization	Tumor location	Adjuvant treatment	Patient numbers			Median overall survival (mos)		*P* value
					Total	No adjuvant	Adjuvant	No adjuvant	Adjuvant	
Agrawal[37]	1971–2005	Retrospective review, Roswell Park	Small bowel	Chemotherapy	30	19	11	41	56	NR
Kelsey[57]	1975–2005	Retrospective review, Duke University	Duodenum	5-FU/Radiation	32	16	16	44%*	57%*	0.42
Fishman[43]	1986–2004	Retrospective review, Princess Margaret Hospital	Small bowel	Chemotherapy	60	45	15	28	22	NR
Dabaja[36]	1978–1998	Retrospective review, M. D. Anderson	Small bowel	Chemotherapy	120	62	58	36	19	0.49
Klinkenbiji[41]	1987–1995	Randomized phase III, EORTC	Periampullary	5-FU/Radiation	93	49	44	40	40	0.74
Sohn[60]	1984–1996	Retrospective review, Johns Hopkins Hospital	Duodenum	5-FU/Radiation	48	37	11	35	27	0.73

*5-year overall survival
Abbreviations: NR = not reported; EORTC = European Organization for Research and Treatment of Cancer; 5-FU = 5-fluorouracil; mos = months

factors that have been associated with worse outcome in the literature are the presence of Crohn's disease and pathologic evidence of vascular invasion.[12,35]

The pattern of failure for small bowel adenocarcinoma is predominantly systemic (Table 3). In one series of 146 patients who underwent resection, 56 patients relapsed at a median time of 25 months, with sites of recurrence reported as distant in 33 patients, peritoneal carcinomatosis in 11 patients, abdominal wall in 4 patients, and local in 10 patients.[36] In a second study of 30 patients who underwent curative resection for small bowel adenocarcinoma, 21 relapsed, with the most common sites being the liver in 67%, lung in 38%, retroperitoneum in 29%, and peritoneal carcinomatosis in 25%.[37]

Of note, patients with duodenal adenocarcinoma have a higher local failure rate compared with patients with adenocarcinoma of the jejunem or ileum. One study reported a 39% rate of local-regional failure among 31 curatively resected patients.[38] In this study, positive margin status was the strongest predictor of local recurrence, with four out of five patients who had either microscopic or macroscopic positive margins developing local failure. As Table 3 shows, however, distant failure remains the primary pattern of failure for resected adenocarcinomas of the duodenum.

ADJUVANT THERAPY

At present, there is no evidence showing a benefit from the use of adjuvant chemotherapy following curative resection in patients with small bowel adenocarcinoma. All available data, shown in Table 4, are drawn from small single-institution retrospective reports, which are all limited by significant selection bias. In these retrospective studies, it is very likely that those patients selected to receive adjuvant therapy were at highest risk for disease recurrence and therefore represent a group with worse overall prognosis compared to those patients who did not receive any adjuvant therapy. Though not fully detailed in these studies, the mainstay of chemotherapy used for adjuvant treatment was probably single-agent 5-fluorouracil (5-FU).

Despite these negative studies, the primarily distant failure pattern for patients with small bowel adenocarcinoma argues for further investigation of systemic adjuvant therapy. This is particularly true given the marked improvement in activity that has recently been demonstrated with the addition of oxaliplatin to 5-FU in the metastatic setting. Patients with lymph node involvement following curative resection, are at extremely high risk for disease recurrence, with recent series from large academic institutions reporting 5-year overall survival rates of only 22%–27%.[35,39,40] Clearly, a means of improving outcomes for these patients is needed.

The role of radiotherapy as a component of adjuvant therapy for duodenal adenocarcinoma has been studied in a limited fashion. One prospective phase-III study conducted by the European Organization for Research and Treatment of Cancer (EORTC) evaluated the role of concurrent 5-FU and radiotherapy as adjuvant therapy in patients with pancreatic and periampullary carcinoma, which was defined as adenocarcinoma of the distal common bile duct, ampulla of Vater, or duodenum. A total of 93 patients with periampullary cancer were randomized to either observation or concurrent 5-FU and radiotherapy.[41] Five-year overall survival between the two groups was equal.

In a recent series from Duke University, no difference in 5-year overall survival was seen between patients who did or did not receive concurrent 5-FU and radiotherapy as adjuvant or neoadjuvant therapy. However, in the subgroup of patients who had a margin-negative resection (n = 25), 5-year overall survival was 53% in the surgery-alone group and 83% in the chemoradiotherapy group ($P = .07$).[38]

The role of neoadjuvant chemoradiotherapy for duodenal adenocarcinoma has been studied in small numbers. An initial report from Fox Chase Cancer Center reported complete pathologic responses in four of four patients treated with radiotherapy and concurrent 5-FU and mito-

Table 5. Studies of systemic chemotherapy for advanced small bowel adenocarcinoma

Author	Year	Study	No. pts	Chemotherapy	RR (%)	Median OS (mos)
Suenaga[46]	2009	Retrospective review	10	5-FU single agent	10	12
Overman[48]	2008	Prospective phase II	30	CAPOX	50	20.4
Ono[61]	2008	Retrospective review	10	Cisplatin + irinotecan	12.5	17.3
Overman[51]	2008	Retrospective review	29 51	5-FU + platinum Various agents	41 16	14.8 12
Fishman[43]	2007	Retrospective review	44	Various agents	29	18.6
Locher[50]	2005	Retrospective review	20	5-FU + platinum	21	14
Gibson[47]	2005	Prospective phase II	38	FAM	18	8
Enzinger[62]	2005	Prospective phase I	4	5-FU + cisplatin + irinotecan	50	NR
Czaykowski[63]	2007	Retrospective review	16	5-FU based	6	15.6
Goetz[64]	2003	Prospective phase 1	5	5-FU + oxaliplatin + irinotecan	40	NR
Polyzos[65]	2003	Case series	3	Irinotecan	0	NR
Crawley[49]	1998	Retrospective review	8	ECF and 5-FU based	37	13
Jigyasu[66]	1984	Retrospective review	14	5-FU based	7	9
Ouriel[67]	1984	Retrospective review	14	5-FU based	NR	10.7
Morgan[68]	1977	Retrospective review	7	5-FU based	0	NR
Rochlin[45]	1965	Retrospective review	11	5-FU single agent	36	NR

Abbreviations: No. = number; RR = response rate; OS = overall survival; NR = not reported; 5-FU = 5-fluorouracil; FAM = 5-FU/doxorubicin/mitomycin C; ECF = 5-FU/epirubicin/cisplatin; CAPOX = capecitabine/oxaliplatin; mos = months

mycin-C.[42] However, a larger report from Duke University noted complete pathologic responses in only 2 of 11 patients treated with neoadjuvant 5-FU–based chemoradiotherapy.[38] Interestingly, none of these patients had lymph node involvement at the time of surgical resection, though no description of pretreatment radiographic staging was reported.

Despite the lack of evidence supporting the use of adjuvant chemotherapy, data from the National Cancer Data Base demonstrates a dramatic increase in its use, from 8.1% in 1985 to 23.8% in 2005.[2] It is likely that the proven benefit of adjuvant chemotherapy in colorectal cancer is being applied to clinical decision making for patients with small bowel adenocarcinoma. Determining the benefit of adjuvant therapy for this disease will require a prospective randomized trial, which, given the rarity of this cancer, is unlikely to occur. An alternative to this strategy would be to generate larger data sets through the collaboration of multiple academic centers.

SYSTEMIC CHEMOTHERAPY

The benefit of palliative chemotherapy compared to best supportive care has not been evaluated prospectively in this cancer. A number of single-institution retrospective analyses of patients who did and did not receive palliative chemotherapy have shown a survival benefit with the use of palliative chemotherapy.[36,43,44] In the largest series from the Princess Margaret Hospital in Canada, 44 patients with advanced small bowel adenocarcinoma who received palliative chemotherapy had a median overall survival of 18.6 months compared to a median overall survival of 13.4 months in 61 patients who did not receive palliative chemotherapy ($P = .035$).[43] However, part or all of this survival benefit may be related to selection bias. In an attempt to address this concern, the authors noted that no statistically significant difference in performance status existed between the two groups.

In the first report of chemotherapy for the treatment of small bowel carincoma, published in 1965, 4 of 11 patients responded to single-agent 5-FU.[45] Since then, a number of primarily retrospective studies have been conducted to evaluate various chemotherapy combinations for this cancer (Table 5). Single-agent 5-FU remains an active agent for this disease, though it is likely less active than initially thought, with a recent study reporting only one response among 10 treated patients.[46] This is probably explained by the use of more reliable cross-sectional imaging to determine objective tumor responses.

Only two prospective studies have been conducted on this tumor. One multicenter study conducted by the Eastern Cooperative Oncology Group (ECOG) reported on the combination of 5-FU, doxorubicin, and mitomycin C (FAM) in 39 patients with adenocarcinoma of the small bowel or ampulla of Vater. The overall response rate was 18%, with a median overall survival of 8 months.[47]

A second single-institution study conducted at M. D. Anderson Cancer Center evaluated the combination of capecitabine and oxaliplatin (CAPOX) in 30 patients with either metastatic or locally advanced small bowel or ampullary adenocarcinoma. The overall response rate was 50%, with a median time to progression of 9.8 months and a median overall survival of 20.3 months.[48] For the 25 patients with metastatic disease, the response rate was 52%, with a median overall survival of 15.5 months. In the 18 patients who had small bowel adenocarcinoma, the response rate was 61%, with a median time to progression of 9.8 months and median overall survival of 20.4 months. Of note, 10% of treated patients had a complete radiographic response to CAPOX.

Other retrospective studies support the antitumor activity of 5-FU combined with a platinum agent in this tumor type, with reported response rates of 18%–46%.[43,49–51] In one of the largest retrospective studies conducted to date, a total of 80 patients with metastatic disease who received front-line chemotherapy from 1978 to 2005 at M. D. Anderson Cancer Center were analyzed.[51] Twenty-nine patients received 5-FU with a platinum agent (cisplatin in 19, carboplatin in 4, oxaliplatin in 6), 41 patients received 5-FU–based therapy without a platinum (5-FU alone in 32, FAM in 3, other 5-FU combinations in 6), and 10 received non-platinum and non-5-FU–based therapy. When compared to patients receiving a non-platinum–containing regimen, patients who received 5-FU combined with a platinum compound had an improvement in response rate (46% vs. 16%, $P < .01$) and an improvement in median progression-free survival (8.7 months vs. 3.9 months, $P < .01$). Although not statistically significant, there was a trend in median overall survival favoring the combination of 5-FU and a platinum agent (14.8 months vs. 12 months, $P = .1$).

A preliminary report of a retrospective French multicenter study has further confirmed the activity of the FOLFOX (folinic acid/5-FU/oxaliplatin) regimen. In this report, 48 patients with advanced cancer who received FOLFOX as front-line therapy had a median progression-free survival of 7.4 months and median overall survival of 17.8 months.[52]

Irinotecan has demonstrated activity in this disease type, with one retrospective study reporting 5 of 12 patients responding to irinotecan-based therapy — six patients received FOLFIRI (folinic acid/5-FU/irinotecan), two received XELIRI (capecitabine/irinotecan), and four were treated with single-agent irinotecan.[43] A second study of salvage therapy with FOLFIRI in the second-line setting reported stable disease in 4 of 8 patients and a median progression-free survival of 5 months.[50]

Limited data exist regarding other chemotherapy agents. Gemcitabine appears to have some activity, with four of eight patients responding to the combination of gemcitabine and 5-FU.[43] A second study reported a response in the salvage setting with single-agent gemcitabine in one of two treated patients.[51] The role of targeted therapies, such as anti-vascular endothelial growth factor receptor (VEGFR) or anti-epidermal growth factor receptor (EGFR) therapies, has not been evaluated in this cancer.

DISCUSSION

Adenocarcinoma of the small intestine is forty- to fiftyfold less common than adenocarcinoma of the large intestine. The explanation for this dramatic difference in incidence is not known and further research to understand this disparity would likely provide insights into the mechanisms of carcinogenesis at both sites. The use of wireless capsule endoscopy has greatly facilitated the workup of small bowel malignancy, and approximately 5%–10% of patients evaluated for obscure gastrointestinal bleeding will have a small bowel tumor.

Following curative resection, patients with lymph node involvement or positive margins have a particularly poor outcome. Only a limited number of single-institution retrospective studies have evaluated the role of adjuvant chemotherapy. None of these studies have demonstrated a benefit with adjuvant chemotherapy, though small sample sizes and the retrospective nature of these analyses limit the interpretation of these results. In patients with resected margin-negative duodenal adenocarcinoma, one retrospective study suggested a benefit from adjuvant 5-FU–based chemoradiotherapy.

Systemic chemotherapy for patients with advanced disease appears to provide a survival benefit, and encouraging median survivals in the range of 14 to 20 months have been seen with modern chemotherapy combinations. Capecitabine or infusional 5-FU combined with oxaliplatin appears to be one of the most active combinations and should be considered for the front-line treatment of patients with this cancer. Improved outcomes with modern chemotherapy combinations in patients with advanced disease are encouraging, but further research and improved treatments for this orphan malignancy are needed.

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Disclosures of Potential Conflicts of Interest

Dr. Overman holds a research grant from sanofi-aventis.